UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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Memorandum

Subject: Chlorpyrifos Methyl: Toxicology Section of the RED Chapter

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Attached is the Toxicology Section of the RED for chlorpyrifos methyl. An electronic copy is available for insertion into the RED.

Copies of the HIARC report dated *pending*

Also attached is APPENDIX 1. Updated Executive Summaries for Selected Toxicity Studies.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile or Toxicology Assessment

Attachment 1 presents the results of the most recent HIARC report and is more comprehensive than HIARC reports dated October 20, 1997 and July 8, 1998.

Currently there are data gaps for the following studies. Inclusion of the study as a data gap below implies that there is no acceptable study conducted under current guideline protocols for the listed study type.

§ 81-1 (870.1100)	Acute oral toxicity-Rat
§ 81-2 (870.1200)	Acute dermal toxicity -Rabbit
§ 81-3 (870.1300)	Acute inhalation study- Rat
§ 81-4 (870.2400)	Primary ocular irritation-Rabbit
§ 81-5 (870.2500)	Primary dermal irritation-Rabbit
§ 81-6 (870.2600)	Dermal sensitization study- Guinea pigs
§ 81-7 (870.6100)	Delayed neurotoxicity study - Hens
§ 81-8 (870.6200)	Acute neurotoxicity study - Rat
§ 81-2 (870.3200)	Subchronic dermal toxicity study - Rat or Rabbit
§ 82-4 (870.3465)	Subchronic inhalation study -Rat
§ 82-7 (870.6200)	Subchronic neurotoxicity study -Rat
§ 83-1 (870.4100)	Chronic toxicity-Dog
§ 83-3b(870.3700)	Prenatal developmental neurotoxicity study - Rabbit
§ 83-4 (870.3800)	Two-generation reproduction study - Rat
§ 83-6 (870.6300)	Developmental neurotoxicity study -Rat
§ 85-1 (870.7485)	General metabolism-Rat
§ 85-2 (870.7600)	Dermal Absorption

Table 1 presents the acute toxicity of chlorpyrifos methyl. The acute toxicity data are based on studies conducted in the 1960s or in some cases early 1970s. The acute toxicity data base need to be updated with studies using modern protocols. The available data indicate that chlorpyrifos methyl is moderately toxic (Toxicity Category III) by the oral and dermal routes. There is no dermal sensitization study.

Table 1. Acute Toxicity of Chlorpyrifos methyl

Guideline No.: and Study Type	MRID #	Results	Tox Category
81-1. (870.1100) Acute Oral-rat	242152	LD_{50} in corn oil: = 2140 (1530-2990) mg/kg for males = 1090 (694-1710) mg/kg for females [Note: 1969 Supplementary study]	III
81.2. (870.1200) Acute Dermal-rabbit	242152	LD_{50} > 2000 mg/kg. [Note: 1964 MINIMUM study]	III
81.3. (870.1300) Acute Inhalation		No valid study with technical grade.	
81.4. (870.2400) Primary Ocular-rabbit	242152	Slight irritation in all eyes. Clearing 5/6 rabbits in seven days. [Note: 1974 MINIMUM study]	III
81.5. (870.2500) Primary Dermal-rabbit	242152	No modern study. Classified as having irritation in 2/3 rabbits on days 4-7 exposure. [Note: 1964 MINIMUM study]	III
81.6. (870.2500) Sensitization-guinea pig	44906901	Study is UNACCEPTABLE.	
81.7. (870.6100) Neurotoxicity - hens	00029503	Study is classified as UNACCEPTABLE- not UPGRADEABLE. A repeat study is required to resolve the equivocal nature of the results.	
81.8 (870.6200) Neurotoxicity screen - rats		No Study.	

The subchronic, chronic , developmental, carcinogenicity, mutagenicity and metabolism data base is presented in Table 2.

Table 2. Toxicity Profile of Chlorpyrifos Methyl

Study Type	MRID No.:	Results
82-2. 21-day dermal - rats		No study.
82-1. Subchronic feeding - rats	44906902 45048301	Plasma Cholinesterase: NOAEL = 0.1 mg/kg/day LOAEL = 1 mg/kg/day RBC Cholinesterase: NOAEL = 1 mg/kg/day LOAEL = 10 mg/kg/day Systemic: NOAEL = 1 mg/kg/day LOAEL = 10 mg/kg/day (based on pathology of the adrenal -hypertrophy, vacuolation and necrosis).
82-1. 28-day feeding - mouse	44668202	NOAEL (ChE inhibition) = 0.141 mg/kg/day **&** and 0.65 mg/kg/day **%**. LOAEL (ChE inhibition) = 0.745 mg/kg/day **&** and 1.27 mg/kg/day **%**.
82-1. Subchronic feeding -dog	44680601	NOAEL (ChE inhibition) = 0.1 mg/kg/day both sexes. LOAEL (ChE inhibition) = 10 mg/kg/day both sexes.
82-4. Subchronic inhalation - rats		No study.
83-1. Chronic feeding - dog	Accession No.: 242154 or 33832	Study classified as unacceptable on 4/7/98..
83-5 Chronic/ carcinogenicity - rat	42269001	NOAEL (ChE inhibition) = 0.1 mg/kg/day LOAEL (ChE inhibition) = 1 mg/kg/day No evidence of carcinogenicity.
82-2. Carcino-genicity -mouse	44680602	NOAEL(ChE inhibition) = 0.403 mg/kg/day (**&**) and 0.418 mg/kg/day (**%**). LOAEL (ChE inhibition) = 3.94 mg/kg/day (**&**) and 4.40 mg/kg/day (**%**) NOAEL (systemic) = 3.94 mg/kg/day (**&**) and 4.40 mg/kg/day (**%**) LOAEL (systemic) = 41.5 mg/kg/day (**&**) and 44 mg/kg/day (**%**) liver kidney and adrenal and body weight effects.
Developmental toxicity - rat	44680603	Maternal toxicity: NOAEL = 1.0 mg/kg/day. LOAEL = 12.5 mg/kg/day based on decreased RBC ChE. Developmental toxicity: NOAEL $\geq$ 50 mg/kg/day (no effects at highest dose tested)
Developmental toxicity - rabbit/oral		No acceptable study.
Reproductive toxicity - rat	00030757 099640 242150	Study classified as Unacceptable not upgradeable.

Study Type	MRID No.:	Results
Gene Mutation-Ames test	41887601	No evidence of mutagenicity ± metabolic activation (S9).
In vitro cytogenetics in CHO cell cultures	00154130	No evidence of clastogenic effect in the absence of metabolic activation. Inthe presence of metabolic activation (S9), there was a positive response at dose levels of 15 and 50 Fg/mL.
Gene mutation assay in CHO cells in culture	00146053	No evidence of mutagenic effects.
Micronucleus assay *in vivo*	00145108	No evidence of clastogenic or aneugenic effect in either sex.
Unscheduled DNA synthesis *in vitro*	00145107	No evidence of genotoxic response.
General metabolism	00029484	Study classified as unacceptable and not upgradeable. Uses only two males in a preliminary study.
Dermal penetration		No study.

3.1 Hazard Profile.

Chlopryrifos methyl is an organophosphate insecticide and inhibition of plasma and/or red blood cell (RBC) cholinesterase was established as the critical endpoint for risk assessment. The dose levels selected for risk assessment did not show classical signs of cholinergic symptoms which were evident only at higher doses. Other systemic toxicity included body weight loss, decreased food consumption, liver, kidney and adrenal pathology. The potential for chlorpyrifos methyl to induce delayed type neurotoxicity remains open because the acute study was considered equivocal and a repeat study is being requested. A subchronic hen study did not indicate delayed type neuropathy in hens at dose levels up to and including 500 mg/kg/day.
Neither the rat or the mouse carcinogenicity studies were interpreted as being positive for induction of neoplasia and HIARC has classified chlorpyrifos methyl as “not likely to be a human carcinogen”. Developmental toxicity assessment is considered incomplete because there is only a rat study but no acceptable rabbit (or second species) study and there is no acceptable multi-generation reproduction study. Since the developmental toxicity data base is incomplete the assessment for increased susceptibility to fetuses and neonates is also incomplete. There is also no general metabolism study that adequately assess the uptake, distribution, retention and excretion or identification of metabolites. The mutagenicity data base conforms to current standards and was noted to be positive only in an *in vitro*

cytogenic assay in the presence of metabolic activation.